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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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11/25/2003

Jun Nakamura

US-110

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38108

7590

09/12/2006

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EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 09/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/720,177	Applicant(s) NAKAMURA ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 8-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11/25/03 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>4/6/04, 5/24/04, 6/15/04, 12/22/04</u> | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of the Application

Claims 1-11 are pending.

Applicant's election with traverse of Group I, claims 1-7 drawn to a bacterium modified to reduce glutaminase activity, as submitted in a communication filed on 6/30/2006 is acknowledged.

Applicant's traverse is on the ground(s) that it would not pose an undue burden on the Examiner to examine all the claimed inventions.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement. As previously indicated the claimed inventions have acquired a separate status in the art because of their recognized divergent subject matter, as shown by their different classification. Moreover, it would be false to assume that references teaching a glutaminase synthetase gene would teach a bacterium where the glutaminase activity of the bacterium is reduced or a method to produce L-glutamine. Thus, a comprehensive search of all inventions would require patent/non-patent literature searches which are not co-extensive, class/subclass searches which are not co-extensive, as well as sequence searches. In view of the fact that searches for each of the claimed inventions are not co-extensive, a comprehensive examination of all groups would impose an undue burden on the Examiner.

The requirement is deemed proper and therefore is made FINAL.

Claims 8-11 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-7 are at issue and are being examined herein.

Priority

1. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to JAPAN 2002-342287 filed on 11/26/2002. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on 4/6/2004, 5/24/2004, 6/15/2004, and 12/22/2004 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Drawings

3. The drawings submitted on 11/25/2003 have been reviewed and are accepted by the Examiner.

Claim Objections

4. Claim 2 is objected to because of the following informalities: the term “a chromosome” should be replaced with “the chromosome” as the bacterium is expected to have a single chromosome. Appropriate correction is required.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-7 are directed to a coryneform bacterium which has reduced glutaminase activity and enhanced glutamine synthetase activity. The claims as written do not sufficiently distinguish over coryneform bacterial cells found in nature which have reduced glutaminase activity and enhanced glutamine synthetase activity because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject

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matter. See *Diamond v. Chakrabarty*, 447 US 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of “isolated” or “purified” as taught by Example 4, pages 28-32, of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 4 is indefinite in the recitation of the term “glutaminase activity is similar to or less than” for the following reasons. The term “similar” is a relative term. The term is not defined in the claim and the specification does not provide a standard for ascertaining the requisite degree, such that one of ordinary skill in the art would be reasonably apprised of the scope of the invention. For examination purposes, no patentable weight will be given to the term “similar”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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Claim 1 is directed to a genus of coryneform bacteria modified by any means such that the glutaminase activity in said bacteria is reduced. Claim 2 is directed to the genus of coryneform bacteria of claim 1 wherein the glutaminase activity is reduced by disruption of a genus of glutaminase genes.

Claim 3 is directed to the genus of coryneform bacteria of claim 1 wherein the glutaminase activity is 0.1

U/mg of cell protein or less. Claim 4 is directed to the genus of coryneform bacteria of claim 1 wherein the glutaminase activity is less than the glutamine synthetase activity when measured as activity per unit weight of cellular protein. Claim 5 is directed to the genus of coryneform bacteria of claim 1 wherein

glutamine synthetase activity is enhanced by any method. Claims 6-7 are directed to the genus of coryneform bacteria of claim 5 wherein the glutamine synthetase activity is enhanced by increasing the expression of a genus of glutamine synthetase genes, wherein said increase in expression is obtained by increasing the copy number of the genes or by modifying expression regulatory sequences in said genes.

See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are

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representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require an extremely large genus of genes encoding a glutamine synthetase and a large genus of genes encoding glutaminases. In addition, the claims require unknown methods to decrease/increase the enzymatic activity of a protein, such as (1) mutations in the coding region of a gene encoding the protein which would increase/decrease its enzymatic activity, (2) the presence of enhancers/inhibitors of that enzymatic activity which can be chemicals or the products of other genes, (3) mutations in the regulatory region of a gene encoding said protein, and (4) the presence of transcription inhibitors/enhancers which can be chemicals or the products of other genes.

While the specification and/or the art disclose the *C. glutamicum* genes encoding a glutaminase and a glutamine synthetase (glnA), inactivating deletions of the *C. glutamicum* glutaminase gene which would result in an inactive glutaminase, and increase in the enzymatic activity of the *C. glutamicum* glnA gene product (glutamine synthetase) by increasing the copy number of the *C. glutamicum* glnA gene, the specification fails to disclose the structure of other genes from coryneform bacteria encoding other glutaminases, the structure of other genes from any source encoding glutamine synthetases, or other methods to reduce/enhance enzymatic activity beyond inactivating deletions or increasing the copy number of the gene of interest.

The claims require a genus of genes which are structurally unrelated. A sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of DNAs required in the claimed cell, and there is no information as to a correlation between the structures disclosed/known in the art and the required enzymatic activity. Furthermore, while one could argue that the structures of known

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glutaminases and glutamine synthetases and their corresponding DNAs are representative of all members of the genus of DNAs required, such that the claimed invention is adequately described, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms β -ketoacyl synthase into a malonyl decarboxylase and completely eliminates β -ketoacyl activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with the enzymatic activity required has been provided, one cannot reasonably conclude that the known structures are representative of all the DNAs required in the claimed invention.

Due to the fact that the specification only discloses (1) the *C. glutamicum* glnA gene and its product (glutamine synthetase), (2) a *C. glutamicum* gene encoding a glutaminase (SEQ ID NO: 1), and (3) a single method to reduce enzymatic activity and a single method to increase enzymatic activity, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

12. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *C. glutamicum* cell wherein said cell has been modified to reduce glutaminase activity and to increase glutaminase synthetase activity, wherein the reduction in glutaminase activity is due to an inactivating deletion in the *C. glutamicum* glutaminase gene of SEQ ID NO: 1, and the increase in glutaminase activity is due to an increase in the copy number of the *C. glutamicum* glnA gene, does not reasonably provide enablement for (1) a coryneform bacterium modified in any way to (i) reduce glutaminase activity in said bacterium, and/or (ii) increase glutaminase synthetase activity in said

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bacterium, or (2) a coryneform bacterium wherein the glutaminase synthetase activity is increased by (i) increasing the copy number of any gene encoding a glutaminase synthetase activity, or (ii) any modification in the expression regulatory region of any gene encoding a glutaminase synthetase activity, (3) or any coryneform bacterium modified by disrupting a glutaminase gene in said bacterium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-7 are so broad as to encompass (1) coryneform bacteria modified by any means such that the glutaminase activity in said bacteria is reduced, (2) any coryneform bacterium wherein the glutaminase activity is reduced by disruption of a glutaminase gene, (3) coryneform bacteria modified by any means such that the glutaminase activity is either 0.1 U/mg of cell protein or less, or the glutaminase activity is less than the glutamine synthetase activity when measured as activity per unit weight of cellular protein, (4) the coryneform bacteria of (1) further comprising enhanced glutamine synthetase activity by any method, including increasing the copy number of any gene encoding a glutamine synthetase, and any modification in the regulatory region of any gene encoding a glutamine synthetase. See Claim Rejections under 35 USC §112, second paragraph for claim interpretation.

The enablement provided is not commensurate in scope with the claims due to the extremely large number of genes encoding glutamine synthetases and glutaminases for which there is no structure

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disclosed, as well as the unknown methods which would result in (1) a coryneform bacterium to have reduced glutaminase activity, (2) a coryneform bacterium to have enhanced glutamine synthetase activity, (3) a coryneform bacterium to have glutaminase activity which is 0.1 U/mg cellular protein or less, and (4) a coryneform bacterium to have glutaminase activity which is less than glutamine synthetase activity. In the instant case, the specification enables a *C. glutamicum* cell wherein said cell has been modified to reduce glutaminase activity and to increase glutamine synthetase activity, wherein the reduction in glutaminase activity is due to an inactivating deletion in the *C. glutamicum* glutaminase gene of SEQ ID NO: 1, and the increase in glutaminase activity is due to an increase in the copy number of the *C. glutamicum* glnA gene.

The amount of direction or guidance presented and the existence of working examples. The specification discloses a mutant *C. glutamicum* cell which has an inactivating deletion in the *C. glutamicum* gene comprising SEQ ID NO: 1 (pages 25-27) and is further transformed with the *C. glutamicum* glnA gene to increase the copy number of the glnA gene (pages 28-30), as a working example. However, the specification fails to disclose (1) other methods to obtain a coryneform bacterium which would have reduced glutaminase activity or enhanced glutamine synthetase activity, (2) the structures of other genes encoding any glutamine synthetase activity, (3) the structures of other genes from coryneform bacteria which encode glutaminases, (4) which species within coryneform bacteria have genes encoding glutaminases having sufficient structural similarity with the *C. glutamicum* gene of SEQ ID NO: 1 such that they can have their glutaminase genes disrupted using the *C. glutamicum* gene of SEQ ID NO: 1, or (5) other methods to modify a coryneform bacterium such that the glutaminase activity is 0.1 U/mg cell protein or the glutaminase activity is less than glutamine synthetase activity.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of the coding region of a polynucleotide encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the

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specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any nucleic acid encoding a glutamine synthetase or any nucleic acid from coryneform bacteria encoding a glutaminase. Furthermore, the neither the specification nor the art provide any teaching or guidance as to how the structures of those glutaminases and glutamine synthetases known in the art correlate with that enzymatic activity such that one of skill in the art would know which structural modifications are required to obtain the desired effect in glutaminase and glutamine synthetase activity (i.e., reduction or enhancement). The art clearly teaches that structural changes in a protein to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all genes encoding glutamine synthetases or all genes encoding glutaminases in coryneform bacteria. In addition, it was not routine in the art to screen by trial and error for (1)

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essentially an infinite number of mutations in either the regulatory region of a gene or in the coding region of a gene to determine which ones result in reduced glutaminase activity or enhanced glutamine synthetase activity, as recited in the claims, (2) all possible inhibitors/enhancers of glutaminase/glutamine synthetase activity such as chemicals and the products of other genes, or (3) all possible transcription inhibitors/enhancers of genes encoding glutaminases/glutamine synthetases such as chemicals and the products of other genes. In the absence of (1) a correlation between structure and the required enzymatic activity, (2) some guidance as to the structural changes required in any glutamine synthetase or any glutaminase from coryneform bacteria which would result in a decrease/increase of their enzymatic activity, (3) some guidance as to the structural changes required in the regulatory elements of any gene encoding a glutaminase or any gene from coryneform bacteria encoding a glutaminase such that the synthesis of the gene products can be modulated (i.e., increase or reduction), (4) some guidance as to the structure of modulators (enhancers/inhibitors) of the required enzymatic activity, and (5) some guidance as to the structure of molecules capable of inhibiting/enhancing transcription of genes encoding glutaminases/glutamine synthetases, one of skill in the art would have to test a large number of nucleic acids to determine which ones encode proteins having glutamine synthetase and glutaminase activity, and test an essentially infinite number of modifications to determine which ones would increase/decrease the enzymatic activity of glutamine synthetases and glutaminases.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-2, 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura et al. (EP 1229121 A2 published 8/7/2002; cited in the IDS) in view of Pompejus et al. (WO 01/00843, published 1/4/2001; cited in the IDS) and further in view of Duran et al. (Microbiology 141:2883-2889, 1995). Nakamura et al. teach a method for producing L-glutamine by fermentation of an L-glutamine producing *C. glutamicum* cell, wherein said cell has been modified to increase the intracellular concentration of glutamine synthetase by increasing the copy number of the *glnA* gene of *C. glutamicum* (encodes glutamine synthetase; Example 1, Table 1, strain AJ12418/pGS). Nakamura et al. also teach a method for production of L-glutamine and suppression of L-glutamic acid as a by-product (paragraph [005]-[006]). Nakamura et al. does not teach a method for producing L-glutamine wherein glutaminase activity is reduced. Duran et al. teach that glutaminase degrades glutamine to yield glutamate and ammonium (page 2884, left column, first full paragraph) and disclose a mutant *R. etli* (LM16) wherein

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the chromosomal glutaminase gene is disrupted by Tn5 mutagenesis (Page 2884, Methods, Strains and plasmid). The reference also teaches that LM16 produces more glutamine than glutamate when cultured with different substrates (page 2886, Table 1). As shown in Table 1, the amount of glutamine produced varies from 53X (49/0.9) to 2X (0.8/0.4) more glutamine in the glutaminase deficient mutant LM16 as compared to the wild type *R. etli*. Duran et al. do not teach a *C. glutamicum* or coryneform bacterium glutaminase deficient mutant. Pompejus et al. teach *C. glutamicum* genes encoding glutaminase and glutamine synthetase (Table 1, page 56, Glutamate and Glutamine metabolism, RXA00335 and RXN03176), Pompejus et al. also teach that the disclosed *C. glutamicum* genes can be used for the modulation of production of amino acids (page 11, lines 20-25) and that glutamine is used in both pharmaceutical and cosmetics industries (page 13, lines 17-19). Pompejus et al. do not teach a mutant coryneform bacterium wherein the glutaminase activity in said bacterium has been reduced and the glutamine synthetase activity has been enhanced.

Claims 1-2 are directed in part to a coryneform bacterium that produces L-glutamine modified such that the glutaminase activity of said bacterium is reduced by disrupting the glutaminase gene on the chromosome. Claims 5-7 are directed in part to the coryneform bacterium of claim 1 wherein said bacterium is further modified to increase glutamine synthetase activity in said bacterium by increasing the copy number of the gene encoding said glutamine synthetase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the *C. glutamicum* cell of Nakamura et al. by introducing a deletion mutation in the gene encoding glutaminase, as taught by Duran et al. A person of ordinary skill in the art is motivated to construct such *C. glutamicum* cell in view of the fact that (1) Duran et al. teach an increase in L-glutamine production when the glutaminase gene is disrupted, (2) Pompejus et al. teach that L-glutamine is a chemical used in the pharmaceutical and cosmetics industries, (3) Duran et al. teach that glutaminase degrades L-glutamine to glutamate, and (4) Nakamura et al. teach a method for the production of L-

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glutamine where a reduction in the production of L-glutamic acid is desired. One of ordinary skill in the art has a reasonable expectation of success at further modifying the cell of Nakamura et al. such that the glutaminase gene is disrupted in view of the fact that Pompejus et al. teach the glutaminase gene and inactivation of genes by deletion if the sequence of the target gene is known is well known and widely practiced in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

16. No claim is in condition for allowance.

17. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652